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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTORNEY DOCKET NO.
08/913,555	09/19/97	KAYAGAKI	N	715-118

HM11/0528

LOWE PRICE LEBLANC & BECKER
99 CANAL CENTER PLAZA
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EXAMINER	
TUNG, M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/28/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Pat nts

Office Action Summary	Application No. 08/913,555	Applicant(s) Kayagaki, et al.
	Examiner Mary Tung	Group Art Unit 1644

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *51-154* is/are pending in the application.

Of the above, claim(s) *63-72 and 76-153* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *51-62, 73-75, and 154* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1 and 4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply the Sequence Rule

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Effective February 7th, the Group and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644, Group 1640, Technology Center 1600.

2. The numbering of claims is not accordance with *37 C.F.R. § 1.126*. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with *37 C.F.R. § 1.121(b)*, they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

3. Misnumbered claims 1-104 have been renumbered as claims 51-154, respectively.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

5. The specification discloses the sequences of SEQ ID NOS: 1-31. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Election/Restriction

6. Restriction is required under 35 U.S.C. 121 and 372.

7. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

8. In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

9. Group I, drawn to monoclonal antibodies which reacts with Fas ligand, method of using the monoclonal antibody to inhibit apoptosis and a method of making monoclonal antibodies, claims 51-65, 69-78, 82-85, 87, 88, 90, 91, 93, 94, 96, 97, 99, 100, 102,

103, 105, 106, 108, 109, 111, 113, 115, 117, 119, 121, 123, 124, 126, 127, 129, 130, 132, 133, 135, 136, 138, 139, 141, 142, 144, 145, 147, 148, 150, 151, 153, and 154, classified in class 530, subclasses 387.7 and 413, class 435, subclasses 70.21, 330 and 375.

10. Group II, drawn to DNAs and RNAs, claims 86, 89, 92, 95, 98, 101, 104, 107, 110, 112, 114, 116, 118, 120, 122, 125, 128, 131, 134, 137, 140, 143, 146, 149, and 152, classified in classes 536 subclass 23.53.

11. Group III, drawn to a method for detecting Fas ligand, claims 66-68 and 79-81, classified in class 435, subclass 7.92, class 436, subclass 524.

12. The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

13. Groups I and II are unique products. They differ with respect to their structures and physicochemical properties and are therefore patentably distinct.

14. Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the monoclonal antibody can be used for protein purification by affinity chromatography.

15. Because a search of any or these three distinct inventions would not be co-extensive with a search of the others, an examination and search of two or more inventions in a single application would constitute a serious undue burden on the Examiner.

16. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

17. This application contains claims directed to more than one species or embodiments of the generic invention. These species or embodiments are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

18. Irrespective of whichever group applicant may elect, applicant is further required under 35 U.S.C. 121:

19. To elect a **specific monoclonal antibody** if group I or Group III is elected or to elect a specific DNA or RNA if Group II is elected.

20. Applicant is required, in response to this action, to elect a specific embodiment to which the claims shall be restricted if no generic claim is finally held to be allowable. The response must also identify the claims readable on the elected embodiment, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

21. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional embodiments which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected embodiment. MPEP § 809.02(a).

22. The embodiments listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the embodiments lack the same or corresponding special technical features for the following reasons:

23. The various monoclonal antibodies, DNA or RNAs are unrelated products. They differ with respect to their structures and physicochemical properties and are therefore patentably distinct.

24. During a telephone conversation with Mr. Robert Price on May 6, 1998, a provisional election was made with traverse to prosecute the invention of Group I, claims 51-65, 69-78, 82-85, 87, 88, 90, 91, 93, 94, 96, 97, 99, 100, 102, 103, 105, 106, 108, 109, 111, 113, 115, 117, 119, 121, 123, 124, 126, 127, 129, 130, 132, 133, 135, 136, 138, 139, 141, 142, 144, 145, 147, 148, 150, 151, 153, and 154, and the specific embodiment recited in claims 51-57, the method of using said antibodies, recited in claims 58-60, a kit recited in claims 61 and 62 and a process for making the antibody, recited in claim 154. Affirmation of this election must be made by applicant in responding to this Office action. Claims 63-72 and 76-153 (claims drawn to Groups II and III and non-elected embodiments recited in Group I) are withdrawn from further consideration by the Examiner, *37 C.F.R. § 1.142(b)*, as being drawn to a non-elected invention. Claims 73-75 read on the elected embodiment and will be examined along with claims 51-62 and 154.

25. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with *37 C.F.R. § 1.48(b)* if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under *37 C.F.R. § 1.48(b)* and by the fee required under *37 C.F.R. § 1.17(h)*.

Information Disclosure Statement

26. The information disclosure statement filed 9/19/97 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Reference (1) was submitted without a translation and there was no copy of the reference (6).

Specification

27. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

28. The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

29. The specification on page 7, line 20, page 37, lines 6-10, 13-15, 25 and bridging over to page 38, lines 1, 3-5, 15-18, 20-24 and so forth, is objected to under *37 CFR 1.821(d)* for failing to disclose the Sequence ID number.

30. The use of the trademarks such as "SUPERSCRIPT RTase," page 46, line 17, "APMLITAQ," page 47, line 2, "ALAMAR BLUE," page 52, line 10, page 57, line 1, and page 62, line 13, "GENE PULSER," page 55, line 9, "SUPERDEX," page 59, line 8, and "FLUOROSCAN II," page 62, line 16, and so on, of the specification has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

31. Each letter of the trademarks must be capitalized. *See MPEP 608.01(V)* and *Appendix 1.*

32. The specification is replete with grammatical errors too numerous to mention specifically. The specification should be revised carefully. Examples of such errors are: the meaning of the term "vital body" on page 3, lines 5 and 7 is unknown. The sentences on page 4, lines 1-2 and lines 11-18 are grammatically incorrect and difficult to understand. The specification appears to be a direct translation from the original Japanese patents. The applicants are requested to make any needed grammatical changes.

Claim Rejections - 35 USC § 112

33. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

34. Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

35. It is apparent that the Fas/WR19L cell line recited in claim 54 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of *35 U.S.C. 112*, first paragraph, may be satisfied by a deposit of said cell line. *See 37 CFR 1.802.* The specification does not provide a repeatable method for obtaining the Fas/WR19L cell line and it does not appear to be a readily available material. The reproduction of a cell line from the transfection of the Fas gene is an extremely unpredictable event. The cell line Fas/WR19L, recited in Claim 54, must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the cell line, and it is not

apparent if the cell line is readily available to the public. If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the cell line has been deposited under the Budapest Treaty and that the cell line will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample **or for the enforceable life of the patent whichever is longer.** See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

36. If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the plasmid described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed. Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985), and 37 CFR 1.801-1.809 for further information concerning deposit practice.

37. In addition, the identifying information set forth in *37 CFR 1.809 (d)* should be added to the specification. *See 37 CFR 1.803-1.809* for additional explanation of these requirements.

38. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

39. Claims 52-54, 73-75 and 154 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

40. Claim 52 recites the term "inhibitory activity against apoptosis." Since this phrase includes two negative terms," inhibitory" and "against", it is unclear whether the claim reads on the inhibition of apoptosis or the activation of apoptosis.

41. Claim 53 recites the term "Fas-expressed cells." It is unclear whether the term "Fas-expressed cells" refers to cells which express Fas or have been activated by Fas.

42. Claim 73 recites the phrase "diluting the fused cells with a medium which does not favor unfused myeloma cells to culture the fused cells,". It is unclear how the unfused cells would culture fused cells.

43. Claims 52, 54, 73 and 154 recite limitations within brackets. This renders the claims indefinite since it is unclear whether the preferred embodiment is included inside or outside the parentheses. It is also unclear whether the limitations recited in the parentheses are encompassed by the scope of the claims. It is indefinite to recite "ie" in claim 54.

Claim Rejections - 35 USC § 102 & § 103

44. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

45. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

46. Claims 51-57 and 73-75 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Goodwin ((2), WO 95/18819).

47. The '819 patent teaches monoclonal antibodies that specifically recognize a human Fas ligand (see page 2, lines 27-29, page 3, lines 1-4, page 14 line 35 and bridging over to page 15, line 30, page 16, lines 6-14, page 18, lines 14-21, page 19, lines 3-9, and claims 23-26, in particular). The inhibition of apoptosis is taught on page 1, lines 20-21, page 15 lines 33-14 and page 18 lines 8-13, in particular), a host cell transformed

with the Fas ligand gene and expressing Fas ligand into the culture medium is taught on page 13, lines 30-36, in particular), the use of the monoclonal antibody for affinity purification of Fas ligand is taught (see page 3, lines 13-15 and page 14, lines 17-18 and page 18, lines 5-13, in particular), the detection of Fas ligand in patients with SLE on page 16, lines 14-19, and the detection of Fas ligand in vitro using biotin or avidin on page 17, lines 17-24. The claimed invention appears to be the same or obvious variations of the reference teachings of monoclonal antibodies that specifically recognize the human Fas ligand, the inhibition of apoptosis using the anti-Fas ligand monoclonal antibodies, the production of Fas ligand by transformed cells producing Fas ligand into the culture medium, and the use of monoclonal antibodies for affinity purification of Fas ligand, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the antibodies, *i.e.*, that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed monoclonal antibodies are functionally different from those taught by the prior art and to establish patentable differences. See *in re Best* (562F .2d 1252, 195 USPQ 430 (CCPA 1977) and *ex parte Gray* 10 USPQ2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

48. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

49. Claims 58, 59, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin (WO 95/18819) in view of Harlow (V).

50. The '819 patent has been discussed *supra*. The claimed invention differs from the reference teaching only by the recitation of a method of detection of Fas ligand in a solution using a plurality of monoclonal antibodies. However, the technique recited in the claims is an ELISA procedure using two antibodies which is well known in the art (see Harlow, pages 578-582, 599-604, in particular) and since the '819 patent teaches that Fas ligand is associated with SLE, amongst other autoimmune disorders (see page 16, lines 14-19, in particular), it would be obvious for one of ordinary skill in the art to develop an assay to detect Fas ligand in patients with SLE or other autoimmune

diseases. Harlow (V) teaches the use of a monoclonal antibody immobilized on a carrier ((V) see page 605, in particular) and the other monoclonal antibody that is labeled with an enzyme and the monoclonal antibody which is immobilized is allowed to react with the immobilized antibody ((V) see pages 578-582 and 591-598, in particular). Harlow also teaches the use of biotin-avidin as a detection system ((V) see page 591-592, in particular). One of ordinary skill in the art at the time the invention was made would have been motivated to use the method to detect the Fas ligand in patients with SLE or other autoimmune diseases taught by the '819 patent using the ELISA technique taught by Harlow (V) in order to be able to detect small quantities of Fas ligand in a rapid and easy fashion, quantitatively (see Harlow, page 578, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. Claims 61 and 62 are included because it would be obvious to one of ordinary skill in the art to make a kit comprising the claimed monoclonal antibody and other reagents necessary for clinical detection of Fas ligand, since current clinical laboratory practice requires the use of standardized reagents and procedures available in kits.

51. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin (WO 95/18819) and Harlow (V) as applied to claims 58, 59, 61 and 62 above and further in view of Goding (W).

52. The '819 patent and Harlow have been discussed *supra*. The claimed invention in claim 60 differs from the reference teaching only by the recitation of a method of detection of Fas ligand wherein a purified monoclonal antibody of IgM type is immobilized on a carrier and a Fas ligand in solution is detected by a biotin-labeled monoclonal antibody of IgG type. However, the use of IgM antibodies is well known in the art (see Goding, pages 8, 11-12, in particular). Goding (W) teaches that IgM has potentially 10 binding sites and its functional avidity may be extremely large (see page 12, paragraph 5, in particular). Goding also teaches that an important property of IgG is its interaction with protein A, which provides a useful and efficient method of purifying IgG by affinity column chromatography (see page 15, paragraph 3, in particular). One of ordinary skill in the art at the time the invention was made would have been motivated to use the method to detect the Fas ligand taught by the '819 patent by the ELISA taught by Harlow (V) using the IgM monoclonal antibodies taught by Goding in order to have more binding sites available for antigen binding and using a second biotin-labeled IgG antibody, purified easily in high amounts by protein A agarose, as taught by Goding and detected using the biotin-avidin system taught by Harlow. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

53. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin (WO 95/18819) and Harlow as applied to claims 58, 59 and 61, above and further in view of Takahashi (3).

54. The '819 patent and Harlow have been discussed *supra.* The claimed invention differs from the reference teaching only by the recitation of a kit to detect Fas ligand in the blood of a person with hepatitis. However, Takahashi (3) teaches the expression of high amounts of Fas ligand in mice with hepatitis and the possible correlation with human hepatitis (see page 1567, col. 2, paragraph 2 and bridging over to col. 1, paragraph 1. Since current clinical laboratory practice requires the use of standardized reagents and procedures available in kits, one of ordinary skill in the art at the time the invention was made would have been motivated to use the method to detect the Fas ligand taught by the '819 patent by the ELISA taught by Harlow in patients with hepatitis by using a kit comprising the claimed monoclonal antibody and other reagents necessary for clinical detection of Fas ligand. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

55. Claim 154 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin (WO 95/18819) in view of Smith (X) and further in view of Takahashi (3) and Watanabe-Fukunaga (11).

56. The '819 patent has been discussed *supra.* The claimed invention differs from the reference teaching only by the recitation of the production of the monoclonal antibody reactive with Fas ligand, and the immunosensitizing an animal which does not express a functional Fas molecule. However, the preparation of monoclonal antibodies is well-known in the art (see Smith, page 11.4.1-11.8.2 in particular). Smith (X) teaches the immunosensitization of mice on pages 11.4.2-11.4.5, preparing the antibody producing cells from the immunosensitized mice on pages 11.5.1-11.5.3, mixing the suspension of the antibody producing cells with myeloma cells to fuse both cells on pages 11.6.1-11.7.4, diluting the fused cells with a medium which does not favor unfused myeloma cells to culture, thereby sorting hybridomas produced by the fusion of the antibody producing cells with myeloma cells and then determining whether the antibodies secreted are specific and then cloning the desired antibodies and recloning the desired hybridomas on pages 11.8.1-11.8.2, and preparing the monoclonal antibody from

culture supernatant of the hybridoma or ascites fluid on pages 11.10.1-11.11.5, in particular. Takahashi teaches that mice bearing *lpr* (lymphoproliferation) and *gld* (generalized lymphoproliferative disease) homozygous mutation which do not express Fas or Fas ligand (see page 1567, col. 2, paragraph 1, in particular). Watanabe-Fukunaga (11) teaches the availability of MLR *lpr* mice that lack Fas antigen (see page 314, col. 1, paragraph 2, in particular). Since Takahashi also teaches that when agonistic anti-Fas antibody was administered into (normal) mice, the mice rapidly died of hepatic failure (see page 1567, col. 2, paragraph 2, in particular). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use the mice that do not express Fas or Fas ligand, taught by Takahashi (3) and Watanabe-Fukunaga (11) to raise monoclonal antibodies as taught by Smith to Fas ligand as taught by the '819 patent to avoid having the mice die from the production of anti-Fas ligand antibodies. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

57. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

26. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

26. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Monday through Friday from 8:30 am to 5:30 pm. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

May 27, 1998
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640